REMARKS

Part V Paragraph I. Novelty

In the First Written Opinion the Examiner found that Claims 1-15 and 22 meet the novelty criteria over prior art for concomitant therapy; however, Claims 16-21 and 22 (I believe this is an error and should be Claim 23) lack novelty as being anticipated by Robinson et al. (PNAS 1996). It should be remarked that Claim 16, as filed, is internally disordered. A corrected version of Claim 16 is included herewith. This amendment merely restores the logical order of the claim elements and does not add any new matter.

Compounds covered by major independent Claim 16 and dependent Claims 17-21 as well as Claims 22 and 23 are novel and not known in the prior art. They were derived by Robinson et al. employing a drug design approach, which included use of appropriate pharmacophores as substitutes for key atoms or groups. These substituted novel structures are intended to satisfy the physicochemical, pharmacological, toxicological, biochemical and steric needs (increased receptor interaction) resulting in a much potent drug candidate.

Such a practice is commonplace in the pharmaceutical industry in the development of novel proprietary drugs (from ACE inhibitors to antiviral drugs) derived through molecular modeling or combinatorial chemistry from a proprietary lead compound invented by another. This is why several drugs from different pharmaceutical companies for the same indication have common central core structures and end up as proprietary drugs on the market. As long as the derivation is not obvious or the new entity has unexpected properties, the materials are both novel and non-obvious. For example, diazepam (Roche) and Oxazepam (Wyeth) or the recently introduced thiazolidin-1,4-diones-based antidiabetic drugs troglitazone (Rezulin, Warner Lambert), Rosiglitazone (Avandia, SKB) and Ciglitazone (Actos, Pharmacia Upjohn) are patented compounds even though they have common structural features.

In the present application, the inventors (Robinson et.al.) were the first to screen and isolate active compounds from botanical sources and were the first to show that these compounds blocked HIV Integrase, one of the key enzymes involved in HIV replication. They were the pioneers in initiating the work on Integrase and proceeded

with determination of structure of active compounds. This pioneering work was disclosed in the cited PNAS reference. Subsequently, the inventors designed novel compounds (described in Claims 16-23) emplosying pharmacophoric structural modification to arrive at chemically unique compounds with properties different from the initial lead compounds disclosed in the cited PNAS reference. These new compounds are intended to be pharmacologically/ biochemically more potent and chemically more stable to degradation under *in vivo* conditions. The inventors have departed from the hydroxy acids backbone of the original compounds to the much more polar and ionic amino acid backbone and less polar alkanediols. Also the phenyl group in the chicoric acid esters was modified with 2-and 3-pyridyl, 2-furyl, 2-thienyl, 2-pyrryl and 2-tetralyl, which render completely different physicochemical properties to the compounds, as well as this heteroatom change the shape of the molecule and are expected to have different binding parameters. Since these compounds are not identical to those in the cited reference, Applicants respectfully request that the Written Opinion reflect a finding of novelty for these claims. Claim 16, as submitted, was somewhat garbled. The amended form submitted herewith should make the novelty of the claim more apparent.

Part V Paragraph I. Inventive Step

In the First Written Opinion the Examiner concludes that Claims 1-23 do not show the required inventive step based on the combination of Rideout et.al. (United States Patent No.4,724,232), Babu et.al.(United States Patent No.5,705,647) and Robinson et.al. (PNAS publication discussed above). Applicants respectfully submit thathis argument is flawwed. First of all, the structures in the references have no chemical similarities. Rideout et.al (as well as many other workers) have disclosed nucleoside analogs as specific HIV Reverse Transcriptase inhibitors, whereas Babu et.al. disclose compounds that act as intermediates for the preparation of compounds which inhibit specifically the enzyme HIV Protease, and Robinson et.al. have disclosed the tartaric acid derivatives (chicoric acids) specifically block the enzyme HIV Integrase. When the first two series of compounds were synthesized and shown to be effective against each respective enzyme, the work with HIV Integrase was in its infancy at best. Although all three enzymes are integrally involved in HIV replication, the inventors have shown unequivocally in their specification that the inhibition

mechanism is specific and different and each group of compounds have no inhibitory action on the other two enzymes. For example, the integrase inhibitors covered by the Robinson et.al. invention do not inhibit either Reverse Transcriptase or Protease. Therefore, it is not reasonable to detract from the inventive step of the present invention by lumping these three different classes together as "antiviral medicaments". This is tantamount to negating the inventiveness of any new pharmaceutical by saying that other pharmaceuticals are "organic compounds medicaments" so that any new organic compound cannot be inventive.

Structurally, the three classes of "antiviral medicaments" are extremely different. Most importantly, the combination of these materials shows an unexpected synergistic activity. The combination of three very different classes of drugs can not be predicted. Inhibitors targeted against one enzyme may turn out to be a stimulator rather than an inhibitor of the second enzyme. It is essential to carry out comprehensive biological testing with all three purified enzyme systems to prove that any combination of classes of drugs and more specifically certain drugs in each category are effective in the HIV treatment cocktail. The inventors have tackled this problem successfully and proved that biological testing and inhibition titre values for each individual would be of merit. Not only have the inventors have disclosed novel Integrase inhibitors, but they have also reduced to practice the combination therapy by carrying out sound biochemical testing. Prior to the discovery of the Integrase inhibitors by Robinson et al., the idea of combination of Reverse Transcriptase, Protease and Integrase inhibitors was untested, unproven. Therefore, making the combination, testing it and finding that the combination provides enhanced results is inventive.

Claim Amendments

The claims have been amended to correct the disorganization in Claim 16 (as originally submitted) and to correct certain other typographic errors. These errors include using a small "n" instead of a capital "N" (for nitrogen) in Claim 16 and the omission of carbonyl oxygens in Claim 23. A complete set of "Substitute Sheets" have been included with this document.

Applicants believe that the above amendments have dealt with the Examiner's questioning of novelty for 16-21 and 23 as well as the problems with inventive step for Claims 1-23 (Part V of the Written Opinion). Applicants contends that all the claims are now novel and demonstrate a true inventive step as required by Article 33 (3) PCT and await the Examiner's affirmation of this contention. Any suggestions or recommendations on claim structure are appreciated, and the Examiner is urged to contact the undersigned with any such suggestions.

Respectfully submitted,

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